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Oral Methylnaltrexone Does Not Negatively Impact Analgesia in Patients With Opioid-Induced Constipation and Chronic Noncancer Pain

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INTRODUCTION

- The exact prevalence of opioid-induced constipation (OIC) in patients with chronic noncancer pain (CNCP) is unclear, but it ranges from 40% to ≥90%[1-4]
- OIC can compromise pain management; patients experiencing gastrointestinal (GI) symptoms due to opioids may skip opioid analgesic doses or reduce the dosage, causing inadequate pain control[1,2,5]
- Over-the-counter agents (eg, laxatives) are generally unsatisfactory in relieving OIC[1,2,4,6] because they do not target the underlying pathophysiology of OIC—μ-opioid receptor activation in the GI tract
- Methylnaltrexone is a selective, peripherally acting μ-opioid receptor antagonist that inhibits opioid-induced increases in oral-cecal transit time and time to gastric emptying[7-9]; it has been shown to be efficacious and well tolerated for treatment of OIC when administered subcutaneously[9-11]
- An oral formulation of methylnaltrexone has been developed that is also efficacious and well tolerated for treatment of OIC
  - In one randomized, double-blind, placebo-controlled trial, a significantly greater mean percentage of dosing days with oral methylnaltrexone 300 mg/d (24.6%; $P = 0.001$) and 450 mg/d (27.4%; $P < 0.0001$) versus placebo (18.2%) resulted in rescue-free bowel movements (RFBMs) within 4 hours of dosing during a 4-week once-daily dosing period

OBJECTIVE

- To examine the potential effects of oral methylnaltrexone on centrally mediated opioid analgesia in adults with CNCP and OIC

METHODS

Patient Population and Study Design

- Individuals ≥18 years of age with CNCP for ≥2 months who received ≥50 mg/d of an oral morphine equivalent dose (MED) of an opioid for ≥14 days and had a history of OIC (average of <3 RFBMs per week associated with ≥1 of the following: ≥25% of RFBMs categorized as type 1 or type 2 on the Bristol Stool Form Sale; straining during ≥25% of RFBMs; or ≥25% of RFBMs with a sensation of incomplete evacuation for ≥30 days before screening) were included in the study
- Phase 3, randomized, double-blind, placebo-controlled study with a 14-day (2-week) screening period, a 28-day (4-week) period of once-daily (QD) treatment, a 56-day (8-week) period of as-needed (PRN) treatment, and a 14-day follow-up period
  - Study remained double-blinded throughout
- Patients were randomized to receive oral methylnaltrexone 150 mg/d, 300 mg/d, or 450 mg/d or placebo QD for 4 weeks; during the 8-week PRN period, patients continued to receive the same treatment to which they were assigned at randomization (QD period)

Assessments and Statistics

- Oral MEDs were recorded daily
- Evaluation of pain intensity and opioid withdrawal were conducted at baseline (day 1 predose), 1 hour postdose on day 1 (opioid withdrawal only), days 14 and 28 (QD period), and days 42, 56, and 84 (PRN period)
  - Pain intensity was assessed using an 11-point numerical rating scale evaluating pain during the previous 24 hours (score, 0 = no pain; 10 = worst possible pain)[12]
  - Opioid withdrawal was assessed using the objective opioid withdrawal scale (OOWS)[13]; withdrawal was assessed with and without items related to abdominal cramping
    - Abdominal cramping was considered a potential confounding factor because it may be associated with constipation and is also a frequent outcome associated with methylnaltrexone treatment
    - Higher OOWS scores indicate greater numbers or intensity of symptoms
- The Wilcoxon-Mann-Whitney test was performed to compare changes from baseline in the pain intensity score and OOWS for each oral methylnaltrexone dose versus placebo

RESULTS

- Demographics and baseline characteristics, including pain intensity scores, were generally similar among treatment groups (Table 1)
  - The baseline MED was slightly higher in the oral methylnaltrexone 300 mg/d group versus other groups because 2 patients in the 300 mg group who reported higher daily morphine doses than other patients were included

RESULTS

Table 1. Demographic and Baseline Characteristics

Characteristics		Oral Methylnaltrexone 150 mg/d (n = 201)	Oral Methylnaltrexone 300 mg/d (n = 201)	Oral Methylnaltrexone 450 mg/d (n = 200)	Placebo (n = 201)
Mean age, y (SD)		50.9 (10.3)	51.5 (10.5)	51.4 (10.5)	52.6 (10.3)
Sex, n (%)	Female	133 (66.2)	114 (56.7)	128 (64.0)	130 (64.7)
	Male	68 (33.8)	87 (43.3)	72 (36.0)	71 (35.3)
Race, n (%)	White	164 (81.6)	158 (78.6)	172 (86.0)	166 (82.6)
	Black/African American	30 (14.9)	38 (18.9)	25 (12.5)	27 (13.4)
	Other	7 (3.5)	5 (2.5)	3 (1.5)	8 (4.0)
Primary pain condition, n (%)	Back pain	132 (65.7)	136 (67.7)	135 (67.5)	145 (72.1)
	Arthritis	20 (10.0)	15 (7.5)	19 (9.5)	12 (6.0)
	Neurologic/neuropathic pain	16 (8.0)	13 (6.5)	16 (8.0)	11 (5.5)
	Joint/extremity pain	13 (6.5)	16 (8.0)	11 (5.5)	10 (5.0)
	Fibromyalgia	15 (7.5)	8 (4.0)	11 (5.5)	12 (6.0)
	Other	5 (2.5)	13 (6.5)	8 (4.0)	11 (5.5)
Baseline MED, mg/d*	Median (range)	141.1 (30.0–1280.0)	177.5 (47.4–2289.3)	155.6 (27.0–1272.0)	132.0 (42.6–1077.3)
	Mean (SD)	200.0 (205.2)	252.6 (298.1)	218.0 (189.1)	209.7 (199.1)
Mean pain intensity score (SD)		6.4 (1.8)	6.4 (1.9)	6.4 (1.9)	6.2 (2.1)

*Baseline opioid dose defined as average of daily oral MED during screening (within 30 days of first dose of study drug): calculated as [sum of total oral morphine equivalents during screening] / [number of days during screening].
MED = morphine equivalent dose; SD = standard deviation.

- Pain intensity scores remained stable throughout the 4-week QD and 8-week PRN periods, with no statistically significant differences noted for the 3 oral methylnaltrexone treatment groups versus placebo (Table 2)

Table 2. Changes in Pain Intensity During Treatment With Oral Methylnaltrexone

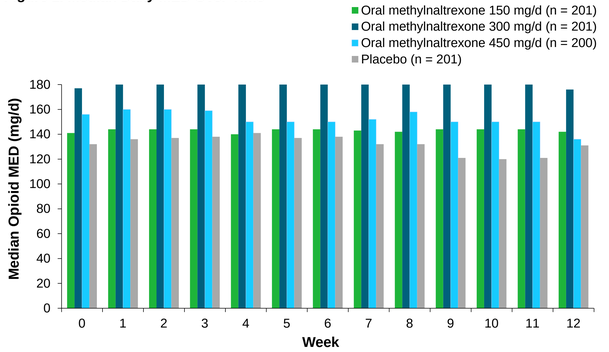
Characteristics		Oral Methylnaltrexone 150 mg/d (n = 201)	Oral Methylnaltrexone 300 mg/d (n = 201)	Oral Methylnaltrexone 450 mg/d (n = 200)	Placebo (n = 201)
Day 14	Mean score (SD)	6.2 (1.9)	6.2 (2.1)	6.4 (1.9)	6.1 (2.0)
	Mean change from baseline	-0.1	-0.1	0.0	-0.1
	Change vs placebo* (95% CI)	0.0 (-0.3, 0.3)	0.0 (-0.3, 0.4)	0.2 (-0.2, 0.5)	
	P value	0.9	0.8	0.3	
Day 28	Mean score (SD)	6.4 (1.8)	6.5 (2.0)	6.3 (1.9)	6.1 (2.0)
	Mean change from baseline	0.1	0.1	0	-0.1
	Change vs placebo* (95% CI)	0.2 (-0.1, 0.5)	0.3 (-0.1, 0.6)	0.1 (-0.2, 0.4)	
	P value	0.2	0.1	0.5	
Day 42	Mean score (SD)	6.4 (1.9)	6.3 (2.0)	6.4 (1.9)	6.2 (2.0)
	Mean change from baseline	0	-0.1	-0.1	-0.1
	Change vs placebo* (95% CI)	0.1 (-0.2, 0.4)	0 (-0.3, 0.4)	0 (-0.3, 0.4)	
	P value	0.6	>0.9	0.9	
Day 56	Mean score (SD)	6.4 (1.9)	6.5 (1.9)	6.4 (2.0)	6.3 (1.9)
	Mean change from baseline	0	0.1	0	0
	Change vs placebo* (95% CI)	0 (-0.3, 0.4)	0.2 (-0.2, 0.5)	0 (-0.4, 0.4)	
	P value	0.8	0.4	>0.9	
Day 84	Mean score (SD)	6.3 (1.9)	6.4 (1.9)	6.3 (2.0)	6.2 (2.0)
	Mean change from baseline	0	0.1	0	-0.1
	Change vs placebo* (95% CI)	0.1 (-0.3, 0.5)	0.2 (-0.1, 0.6)	0.1 (-0.3, 0.4)	
	P value	0.6	0.2	0.7	

*Value reflects least-squares mean difference versus placebo.
CI = confidence interval; SD = standard deviation.

RESULTS

- Minimal changes in median MED in patients with OIC were observed during the 4 weeks of QD dosing and 8 weeks of PRN dosing (Figure 1)
  - Mean MED data were also consistent with minimal changes observed after 4 weeks of QD treatment (range, 214.5–235.6 mg/d) and after 8 weeks of PRN treatment (range, 202.3–234.9 mg/d)

Figure 1. Median Daily MED Over Time

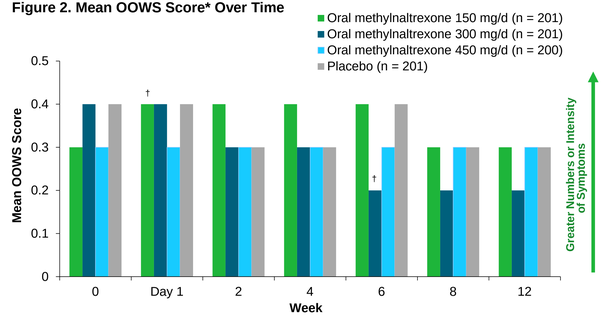


MED = morphine equivalent dose.

RESULTS

- The percentage of patients who initiated new opioid medications during the QD period was generally similar among the oral methylnaltrexone 150 mg, 300 mg, and 450 mg groups (44.8%, 43.3%, and 35.0 %, respectively), the oral methylnaltrexone combined group (41.0%), and the placebo group (39.8%)
  - The most common newly initiated opioid medications during the QD dosing period were oxycodone (oral methylnaltrexone groups combined, 14.6%; placebo, 12.4%) and morphine (oral methylnaltrexone combined, 10.1%; placebo, 7.0%)
- There were minimal mean changes from baseline in OOWS scores, with abdominal cramping assessments included (data not shown) or without (Figure 2), during the 12-week study; changes from baseline were comparable across groups

Figure 2. Mean OOWS Score* Over Time



*Scoring excluded items related to abdominal cramping.
†$P < 0.05$ versus placebo for change from baseline.
OOWS = objective opioid withdrawal scale.

CONCLUSIONS

- **Results show no demonstrable effects of oral methylnaltrexone on centrally mediated opioid analgesia in patients with CNCP and OIC**
- **Data further support that methylnaltrexone can be considered as an option for the treatment of OIC, without clinically significant concerns about compromising pain management strategies in patients with CNCP**

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